European Psychiatric Association Guidance on Psychotherapy in Chronic Depression across Europe.

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Original article

European Psychiatric Association Guidance on psychotherapy in chronic depression across Europe

A. Jobst [a,1], E.-L. Brakemeier [b], A. Buchheim [c], F. Caspar [d], P. Cuijpers [e,1], K.P. Ebmeier [f], P. Falkai [a], R. Jan van der Gaag [g], W. Gaebel [h], S. Herpertz [i], T. Kurimay [j], L. Sabaß [a], K. Schnell [k], E. Schramm [k,1], C. Torrent [l], D. Wasserman [m], J. Wiersma [n], F. Padberg [a,1,*]

[a] Department of Psychiatry und Psychotherapy, Ludwig Maximilian University, Munich, Germany
[b] Department of Clinical Psychology and Psychotherapy, Berlin University of Psychology, Berlin, Germany
[c] Department of Psychology, Clinical Psychology, University of Innsbruck, Innsbruck, Austria
[d] Institute of Psychology, University of Bern, Bern, Switzerland
[e] Department of Clinical Psychology, VU University, Amsterdam, The Netherlands
[f] Department of Psychiatry, Division of Clinical Medicine, University of Oxford, Oxford, United Kingdom
[g] University Medical Centre, St. Radboud, Nijmegen, The Netherlands
[h] Department of Psychiatry und Psychotherapy, Heinrich Heine University Düsseldorf, Medical Faculty, Düsseldorf, Germany
[i] Department of Psychiatry and Psychotherapy, University of Heidelberg, Heidelberg, Germany
[j] Institute of Behaviour Sciences, Semmelweis University, Budapest, Hungary
[k] Department of Psychiatry and Psychotherapy, University of Freiburg, Freiburg, Germany
[l] Clinical Institute of Neuroscience, Hospital Clinic Barcelona, CIBERSAM, IDIBAPS, University of Barcelona, Barcelona, Spain
[m] National Centre for Suicide Research and Prevention of Mental Ill-Health (NASP), Karolinska Institutet, Stockholm, Sweden
[n] Department of Psychiatry, GGZinGeest, Amsterdam, The Netherlands

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ABSTRACT

Purpose: Patients with chronic depression (CD) by definition respond less well to standard forms of psychotherapy and are more likely to be high utilizers of psychiatric resources. Therefore, the aim of this guidance paper is to provide a comprehensive overview of current psychotherapy for CD. The evidence of efficacy is critically reviewed and recommendations for clinical applications and research are given.
Methods: We performed a systematic literature search to identify studies on psychotherapy in CD, evaluated the retrieved documents and developed evidence tables and recommendations through a consensus process among experts and stakeholders.
Results: We developed 5 recommendations which may help providers to select psychotherapeutic treatment options for this patient group. The EPA considers both psychotherapy and pharmacotherapy to be effective in CD and recommends both approaches. The best effect is achieved by combined treatment with psychotherapy and pharmacotherapy, which should therefore be the treatment of choice. The EPA recommends psychotherapy with an interpersonal focus (e.g. the Cognitive Behavioural Analysis System of Psychotherapy [CBASP]) for the treatment of CD and a personalized approach based on the patient's preferences.
Discussion: The DSM-5 nomenclature of persistent depressive disorder (PDD), which includes CD subtypes, has been an important step towards a more differentiated treatment and understanding of these complex affective disorders. Apart from dysthymia, ICD-10 still does not provide a separate entity for a chronic course of depression. The differences between patients with acute episodic depression and those with CD need to be considered in the planning of treatment. Specific psychotherapeutic treatment options are recommended for patients with CD.
Conclusion: Patients with chronic forms of depression should be offered tailored psychotherapeutic treatments that address their specific needs and deficits. Combination treatment with psychotherapy and pharmacotherapy is the first-line treatment recommended for CD. More research is needed to develop more effective treatments for CD, especially in the longer term, and to identify which patients benefit from which treatment algorithm.

* Corresponding author. Tel.: +49 89 440053358; fax: +49 89 440053930.
E-mail address: padberg@med.uni-muenchen.de (F. Padberg).
[1] A. Jobst, E. Schramm, P. Cuijpers, and F. Padberg constituted a core group of 4 authors who developed and wrote the manuscript.

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1. Introduction

About 20 to 30% of major depressive disorders (MDD) have a chronic course and 47% of patients in specialized mental health care have chronic depressive symptoms [1–6]. Three percent to 6% of the adult population in Western countries develop chronic depression (CD) [4,7,8]. The 12-month prevalence of CD, defined as a depressive syndrome lasting longer than 2 years, is 1.5% in the US [9], while lifetime prevalence rates are approximately 3 to 6% in community and primary care samples [10]. CD is one of the leading causes of disability worldwide and represents an increasing burden of disease [11]. Compared with episodic depression, CD is associated with higher economic costs [12] and health care service use [13]. Moreover, CD shows a larger proportion of comorbidities with other psychiatric Axis I and especially Axis II disorders [9], a stronger adverse impact on quality of life [14], increased disability in physical and psychological functioning [9,15] and a higher rate of hospitalization and risk of suicide [6,16]. Treatment options for CD include pharmacological and psychotherapeutic interventions and, in severe and treatment-resistant cases, even stimulation techniques such as electroconvulsive therapy (ECT). CD is more difficult to treat and shows lower response rates [17,18] than acute episodic depression. The aim of this Guidance Paper from the European Psychiatric Association (EPA) is to provide a comprehensive state-of-the-art overview on psychotherapeutic interventions for CD. We critically review the evidence of efficacy for these treatments and present recommendations for clinical applications and research.

1.1. Definition of chronic depression

The fourth edition (text revision) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) of the American Psychiatric Association (APA) [19] classifies depressive disorder as having a chronic course if it lasts more than 2 years. According to DSM-IV-TR (see also Keller et al. [20]), CD can be divided into 4 subtypes:

- dysthymic disorder;
- chronic major depressive disorder (cMDD, i.e. MDD lasting for at least 2 years);
- double depression (MDD superimposed on a dysthymic disorder);
- recurrent MDD with incomplete recovery between episodes.

Over the last few years, experts of the field have stated that these 4 forms of depression might have more similarities than differences [8,21] and proposed that a single diagnosis that combines all subtypes into one diagnosis might be called the "CD spectrum disorders". Consequently, some authors suggest that depressive disorders should instead be divided into acute and chronic forms [6,15]. They also propose that dysthymic disorder and double depression might be one form of depression [22], because 40% of patients with dysthymic disorder are found to have coexisting MDD [23] and 95.1% of patients with dysthymic disorder have a lifetime major depressive episode (MDE) [22]. Moreover, the comorbidity of MDD and dysthymia is one of the most common among DSM-IV disorders (National Comorbidity Survey conducted by Kessler et al.) [24]. Therefore, in DSM-5 the diagnostic entity "persistent depressive disorder (dysthymia)" (PDD) was introduced to clearly distinguish CD from episodic forms of depression. The criterion of duration rather than severity of illness was selected as the discriminating factor between PDD and MDD. In DSM-5, PDD is categorized into 4 entities to identify different courses (Fig. 1): PDD, as defined by symptoms over the last 2 years, (1) with persistent MDE that becomes chronic, (2) with intermittent MDE with current episode, (3) with dysthymic symptoms, and (4) with intermittent major depressive episodes (MDE) without current episode. Moreover, PDD can be classified as mild, moderate and severe. In this guidance paper, we use the term CD rather than PDD because most of the studies on psychotherapy for chronic or persistent depression were published before DSM-5 was introduced. In the future, however, one term should be used consistently in medical practice and research.

The current ICD-10 classification does not allow a chronic course of MDD to be coded in a similar way as DSM-5, so future

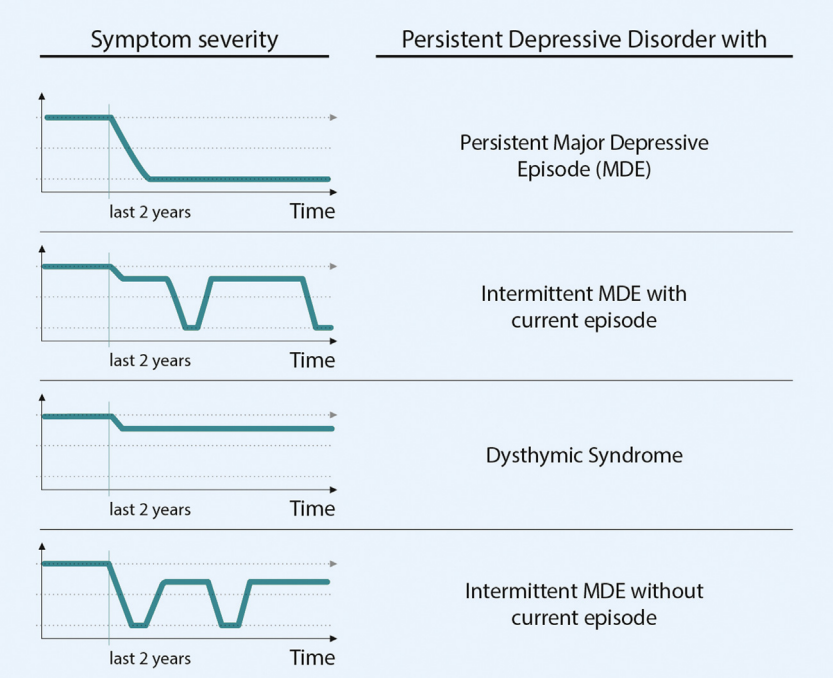

Fig. 1. Clinical presentations of chronic depression (CD) according to DSM-5.

versions of the ICD should implement a separate category for chronic/persistent depression.

For diagnostic evaluation, Lyketsos et al. [25] recommend a Life Chart Interview (LCI) to assess the course of MDD. Patients with CD are mostly (70%) defined by an early onset in adolescence and before the age of 21 years [26–28], leaving around 30% of chronically depressed patients with a late onset of the disorder [28].

Because of their chronic clinical course, approximately 40% of CD patients also fulfil criteria for "treatment-resistant depression" (TRD), which is usually defined by the number of non-successful biological treatments [29]. However, the terms TRD and "difficult-to-treat depression" should be differentiated from CD [30–33] because many patients with CD may have received inadequate pharmacotherapy or psychotherapy or even no treatment at all [34]. In the literature search performed for this guidance paper, we also included the term "treatment-resistant depression", because in some investigations it is used interchangeably with the terms "chronic depression" and "persistent depressive disorder".

1.2. Characteristics of chronic depression

The development and persistence of chronic forms of MDD are often related to adversity and maltreatment experienced during childhood [35–39]. CD patients are more likely than patients with other forms of depression to have a history of multiple childhood trauma [40]; the rate of childhood trauma among CD patients is estimated to be up to 80% [41]. Several studies found an association between family problems in childhood [42], abuse in childhood [43], poor parent–child relationships and chronicity of depression. Moreover, patients with CD have experienced significantly poorer parental care than patients with episodic depression [44] and severity of childhood trauma has been suggested to be associated with chronicity of MDD [39]. Emotional neglect and emotional abuse were found to be the most common subtypes of interpersonal trauma in CD [39,45].

Early childhood adversity and maltreatment are also associated with the development of personality disorders [46–48]. Already in the 1980s and 1990s, CD was discussed as being a form of personality disorder or as being highly associated with personality disorders [49]. Comorbidity with personality disorders in general is high in CD, and CD patients are twice as likely to have comorbid personality disorders [50]. Avoidant personality disorder, borderline personality disorder and antisocial personality disorder are more often found in CD than in episodic MDD [50,51], and avoidant and dependent personality disorders are more often found in CD than in the general population [9]. Moreover, comorbidity rates of anxiety disorders and substance abuse are higher in CD than in episodic MDD [1,52–55]. Klein et al. [51] also showed that emotional abuse had a moderating effect on the association between chronicity of depression and avoidant personality disorder. In addition, personality traits, e.g. neuroticism [56,57], were found to be associated with CD, and specific personality factors such as heightened stress reactivity were described as risk factors for CD [58]. The higher comorbidity of CD than of episodic MDD with personality disorders [9] has been hypothesized to be aetiologically related to the high rate of childhood adversity in CD.

To date, it is not fully understood whether CD constitutes a clinical entity on its own. Distinctive features of interpersonal behaviour have been proposed to represent core characteristics of CD. Indeed, CD patients usually exhibit severe interpersonal problems and deficits, which in general may complicate any psychotherapeutic treatment. Moreover, a novel interactive test of interpersonal behaviour investigated in a recent pilot study allowed CD patients to be differentiated from episodic MDD patients on the basis of their interpersonal deficits. These interpersonal characteristics include being more submissive and hostile than healthy controls [59] and having an avoidant interpersonal style compared with patients with episodic depression [60]. Moreover, problems with the social environment were identified as a risk factor for CD [53] and patients with dysthymic disorder were found to show higher levels of dysfunctional attitudes than patients with episodic depression [58]. These interpersonal problems may follow disturbed attachment, invalidating parenting and interpersonal trauma during childhood, such as emotional neglect [40]. As described by Schramm and Klein [61], early interpersonal insults and trauma may lead to high distrust and social withdrawal. Children of mothers with CD were found to be at greater risk for psychological problems than children of mothers with nonchronic forms of depression [62].

James P. McCullough described an interpersonal model of CD based on the development theory of Piaget [63] in which he proposed that the cognitive-emotional state of CD patients might be compared to the state of children aged between 4 and 7 years ("preoperational") [64], which primarily means that patients are unable to see adverse behaviours by others in the present as consequences of their own behaviour. While the correspondence between CD and the preoperational developmental state is hard to prove, it has been argued that the perspective is useful because therapists who take this perspective are less prone to using interventions beyond patients' abilities [65]. The interpersonal difficulties in CD become predominantly present if patients are personally involved [66,67]. Early adverse interpersonal experiences may have led to this preoperational cognitive-emotional derailment. As a result, patients with CD repeatedly face difficult interpersonal experiences, leading to chronic interpersonal ineffectiveness and instability and ongoing helplessness, which could trigger depressiveness. Dysfunctional interpersonal behaviour might be a perpetuating factor for CD.

Taken together, patients with CD may be distinguished from patients with episodic form of depression not only by difficult-to-treat situations and a chronic course of symptoms, but also by a different aetiology model in which childhood social stress and maltreatment lead to insecure attachment experiences and interpersonal problems in later life.

2. Challenges for psychotherapy

While research on psychotherapy for MDD has a long-standing history, research studies of psychotherapy specifically for CD were first conducted relatively recently, at the end of the 1990s and beginning of the 2000s. Michalak and Lam [68] noted in their 2002 literature review that knowledge about the optimal treatment of CD had been developed rapidly; however, changes in clinical practice had been slower to evolve. Clinical experts have emphasized the importance of a thorough examination of this specific group of depressed patients [6,8,15,21]. CD patients often show a poor therapeutic response to classical types of psychotherapy, e.g. cognitive-behavioural therapy (CBT) and interpersonal therapy (IPT) [17,18,69,70], which can be seen as partly caused by the greater difficulty of establishing a therapeutic relationship [71]. A meta-analysis of 10 clinical trials (that included 3098 participants) revealed that childhood maltreatment is a main factor associated with a lack of response or remission during treatment for depression [72]. Interpersonal dysfunctions in particular seem to play a major role in sustaining a depressive state and are the focus of novel psychotherapeutic approaches [73].

So far, several reviews [2,6,13,70,74–77], systematic reviews [78,79], 1 meta-analysis [80] and 1 network meta-analysis [81] have addressed the efficacy of pharmacological or psychotherapeutic interventions or combined treatment in CD. However,

results are inconsistent and clinical guidelines lack information concerning the efficacy of different psychotherapeutic treatments.

3. Guidance development process

The European Guidance Project (EGP) Guidance Committee (chair W.G.) appointed A.J. and F.P. as the lead authors of this guidance paper. The lead authors were responsible for recruiting further experts to develop the document conceptually. A.J., E.S., P.C. and F.P. constituted the core group of 4 authors who developed, wrote and prepared a draft version of the guideline, which was jointly reviewed and edited by all co-authors before publication. The final version of this guidance paper was reviewed and endorsed by the EGP coordinator (W.G.).

3.1. Systematic literature search

We performed a comprehensive literature search according to the EPA methods, as described in previous publications [82,83]. We searched the *Medline* database by using the medical subject headings (MeSH): ["chronic depression" OR "chronically depressed" OR "persistent depression" OR "treatment-resistant depression" OR "dysthymia"] AND "psychotherapy". With these terms, we identified 2420 citations from January 1977 to January 2015 and screened the titles for compliance with our inclusion criteria (see below). Moreover, we searched the *Cochrane Library* and also examined the reference lists of earlier reviews and meta-analyses on psychotherapy in CD [70,78,80,81] as well as those of existing guidelines on psychotherapy in CD (NICE [84], APA [85], CANMAT [86], DGPPN [87]). Citations were included if they fulfilled the following criteria:

- meta-analysis, randomized controlled trial (RCT), systematic review, cohort study, open study or case series;
- published in English or German;
- published between January 1977 and January 2015;
- examined the effects of psychological treatment on CD (dysthymia, persistent depression, treatment-resistant depression);
- compared the effects of psychological treatment with those of another active treatment or a combined treatment or with a group with no psychological treatment or within a defined cohort;
- intervention tested in adults (18 years or older).

After checking inclusion criteria, 313 abstracts remained and were further screened for relevance by 1 author (A.J.). Of these 313, 227 publications were excluded because they were deemed irrelevant for this statement (studies did not meet all inclusion criteria, including lack of a formal diagnosis, inappropriate study design), or were unavailable or double publications, comments or theoretical papers or written in another language than English or German; the full text of the remaining 86 citations was retrieved. After reviewing the full publications, 35 studies (6 meta-analyses and reviews, 18 RCTs and 11 cohort studies, case series or open studies) were included in the critical review. The flow of articles is outlined in Fig. 2.

3.2. Evidence and recommendation ratings

The methodology of each study was assessed in order to appraise its validity according to the evidence and recommendation grading scheme of the Scottish Intercollegiate Guidelines Network (SIGN) [88]. The results of this quality assessment

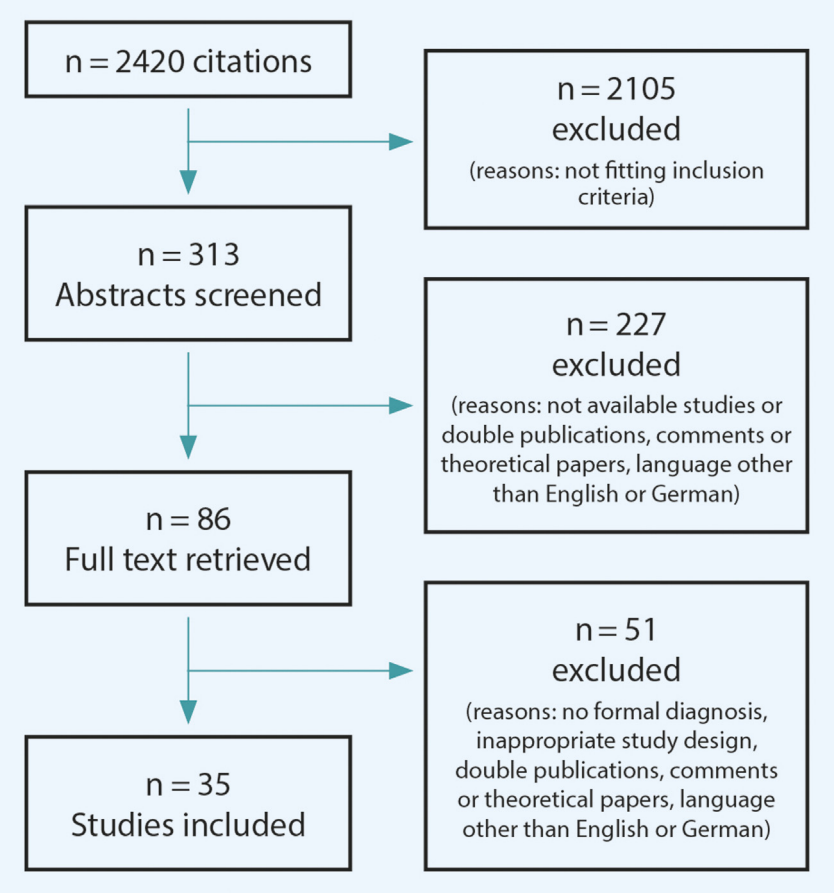

Fig. 2. Flow of articles retrieved by the systematic literature search.

determined the level of evidence for each study (level 1++ to level 4), which in turn influenced the grade of recommendation (grade A to grade D or GPP, as applicable) (Tables 1 and 2). To assess the clinical importance, the guidance development group drafted good practice points during the consensus process on the basis of clinical experience [88] and the EPA checklist for the appraisal of studies' validity [89] and formulated their recommendations. Evidence levels and recommendations were independently rated by all authors of the consensus group.

3.3. Evidence tables (coding of study characteristics and evidence)

The major characteristics of the included studies were recorded, i.e. study type, number, age and gender of participants and the type of psychotherapy used. The type of psychotherapy was classified into the categories: CBT, cognitive therapy (CT), IPT, schema therapy (ST), cognitive-behavioural analysis system of psychotherapy (CBASP), radical openness dialectical behavioural therapy (RO-DBT), mindfulness-based cognitive therapy (MBCT), psychodynamic psychotherapy (PP), brief supportive psychotherapy (BSP) or supportive psychotherapy (SPT) and problem-solving therapy (PST).

The studies included in this review used different definitions of depression chronicity; this heterogeneity hampers the direct comparison of therapeutic effects across studies. Therefore, detailed inclusion criteria for CD are listed for each study included. Outcome and evidence levels are listed in the evidence table (Table 3).

3.4. Consensus process

Recommendations were formally agreed on by the multidisciplinary group of experts and stakeholders. The formal consensus procedure followed the *Delphi method*, i.e. questionnaires were sent to participants and circulated and then a summary form was again sent to the participants for revision.

4. Psychotherapeutic treatment for chronic depression: findings from current guidelines, meta-analyses and systematic reviews

Current national or international clinical guidelines lack information about the efficacy of different types of psychotherapeutic treatment for CD. However, current guidelines on depression in general give some recommendations for patients with residual symptoms or treatment resistance or those who are at risk for relapse. The British National Institute for Health and Care Excellence (NICE) guideline on depression in adults [84] recommends the following for depressed patients "who are considered to be at significant risk for relapse or who have residual symptoms": antidepressant treatment and between 16 to 20 sessions of individual CBT over 3 to 4 months, with 2 sessions in each of the first 2 to 3 weeks, and 5 to 6 additional follow-up sessions over 6 months (for those who have relapsed despite antidepressant medication or have residual symptoms despite treatment) or weekly 2-hour sessions of MBCT in groups of 8 to 15 participants over 8 weeks, with a follow-up after 12 months (for those who are currently well but have experienced 3 or more previous episodes of depression). For complex and severe depression, the NICE guideline recommends a variety of options, i.e. referral to specialist mental health services with complex multi-professional care, inpatient care, crisis resolution, home treatment teams and somatic treatments (e.g. ECT). With regards to psychotherapy, the guideline does not give a specific recommendation, besides the recommendation of a "full range of high-intensity psychological

Table 1
Grading of evidence from questionnaire surveys (quantitative studies), qualitative research (abbreviated and modified from [154]) and reviews.

	Levels of evidence [88]
1 ++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1−[a]	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2 ++	High-quality systematic reviews of case control or cohort studies. High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2−[a]	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Nonanalytic studies, e.g. case reports, case series
4	Expert opinion

[a] Studies graded with 1− or 2− should not be used as a basis for recommendations because of their high risk of bias.

Table 2
Grading of recommendations derived from reviews, quantitative studies (mainly questionnaire-based surveys) and qualitative research.

Modified from the Scottish Intercollegiate Guidelines Network (SIGN, [88]) grading of recommendations, mainly on the basis of intervention studies	
A	At least one meta-analysis, systematic review, or other study rated as I and directly applicable to the target population; or a body of evidence consisting principally of studies rated as I, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as II, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as I or II
C	A body of evidence including studies rated as II–III, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as II–III
D	Evidence level III or IV or Extrapolated evidence from studies rated as III or IV
Modified from the National Institute for Health and Care Excellence (NICE [155]) grading of recommendations	
A	At least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia and Ib) without extrapolation
B	Well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels IIa, IIb, III); or extrapolated from level I evidence
C	Expert committee reports or opinions and/or clinical experiences of respected authorities. This grading indicates that directly applicable clinical studies of good quality are absent (evidence level IV), or with extrapolation from higher levels of evidence
GPP	Good practice point: recommended good practice based on the clinical experience of the Guidance development group and arrived at through consensus

Table 3
Evidence table for included studies (characteristics of studies examining psychotherapeutic treatments for chronic depression): their instruments, population, main results and comments by the guidance authors, including a rating of the evidence level according to the evidence grading scheme shown in Table 2. a) Meta-analyses, reviews; b) Randomized trials; c) Cohort studies, case series, open studies.

a) Meta-analyses, reviews

Bibliographic citation	Inclusion criteria	Interventions /Comparison groups	Comparison groups (*n*)	Primary instrument/ Outcome measures	Main results	Study type and comments	Evidence level
Cuijpers et al. (2010) [80]	CD	1. Control conditions 2. Psychotherapy conditions (CBT, IPT, PST, CBASP, SPT, cognitive-interpersonal group therapy) 3. Combined conditions	167 692 568	Effect sizes of depressive symptom severity rating scale	Small but significant effect for PT compared to control group. PT had smaller effect compared to pharmacotherapy (only for DYST) Combined treatment was more effective compared to other groups	Meta-analysis, but greater proportion of dysthymic samples	1+
Cuijpers et al. (2011) [94]	Subsample of CD	1. Control conditions 2. Psychotherapy conditions (CBT, IPT, BA, SPT) 3. Combined conditions	16 studies	Effect sizes	Smaller PT effects for CD than for nonchronic forms of depression Combined treatment is more effective. In DYST pharmacotherapy is more effective than psychotherapy	Series of meta-analyses	1+
Imel et al. (2008) [95]	Subsample of DYST	1. Medication 2. Psychotherapy	3381	Effect sizes	Both effective for DYST. PT better effects for follow-up than medication. Medication more effective in dysthymia than psychotherapy	Meta-analysis, but subsamples of dysthymic or CD	1+
Kriston et al. (2014) [81]	Persistent depressive disorder (duration longer than 2 years)	1. Medication 2. Psychotherapy (IPT, CBASP)	5806 2657	50% improvement on a symptom severity rating scale	IPT alone was less effective than CBASP and than medication. IPT in combination with medication outperformed medication alone in CD (not dysthymia). CBASP was more effective alone than in combination with pharmacotherapy. Evidence on CBASP plus medication was partly inconclusive	Network meta-analysis	1 ++
Spijker et al. (2013) [78]	CD	1. Psychotherapy (CBT, IPT, CBASP) 2. Pharmacotherapy 3. Combination	2316	Effect sizes of symptom severity rating scale	Best evidence for the treatment of CD for combination treatment, especially with CBASP. Evidence for both alone is very weak	Systematic review	1+
Von Wolff et al. (2012) [79]	cMDD, DYST, MDD +DYST, rMDD incomplete recovery	1. Combined treatment psychotherapy (IPT, CBASP, CBT, SPT) and pharmacotherapy 2. Pharmacotherapy	1618	Standardized mean difference, benefit ratio, odds ratio	Small but significant effects of combined therapies, but no differences between combined treatment and pure pharmacological interventions were observed regarding long-term effects	Systematic review and meta-analysis	1+

Randomized controlled trials

Bibliographic citation	Inclusion criteria of CD	Age of patients, mean	Female patients %	Interventions /Comparison groups	Comparison groups (n)	Primary instrument/ Outcome measures	Main results	Study type and comments	Evidence level
Agosti & Ocepek-Welikson (1997) [99]	Early onset cMDD	31.3	NR	1. CBT 2. IPT 3. Imipramine 4. Placebo	16 14 20 15	HDRS BDI	No difference between treatment and placebo groups	RCT, small sample size, analysis of a subsample	1–
Barker et al. (1987) [101]	cMDD duration longer than 2 years + treatment refractory	49.3	63.6	1. Pharmacotherapy 2. Pharmacotherapy + CBT	10 10	HDRS BDI	No better response outcome for CBT	RCT, small sample size	1–
Barnhofer et al. (2009) [148]	MDD with at least 3 episodes or for longer then 2 years	41.9	67.9	1.MCBT 2.TAU	14 14	BDI-II	MCBT better response rate in the ITT sample	RCT, but small sample size (pilot study)	1–
Barrett et al. (2001) [151]	DYST	44.1	63.9	1. PST 2. Paroxetine 3. Placebo	43 42 42	HDRS HSCL-D	Higher remission rate for paroxetine and PST-PC	RCT	1–

Table 3 (*Continued*)

Randomized controlled trials

Bibliographic citation	Inclusion criteria of CD	Age of patients, mean	Female patients %	Interventions /Comparison groups	Comparison groups (n)	Primary instrument/ Outcome measures	Main results	Study type and comments	Evidence level
Browne et al. (2002) [124]	DYST, 15% had MDD	42.1	68	1. IPT 2. IPT + sertraline 3. Sertraline	178 212 196	MADRS	Best results for combination treatment	RCT, effectiveness study	1–
de Mello et al. (2001) [128]	DYST, 91% had MDD	18–60	80	1. IPT + moclobemide 2. Moclobemide + routine care	16 19	HDRS, MADRS	Significant improvement in both groups, combination treatment better; however, not significant	RCT, small sample size	1–
Dunner et al. (1996) [100]	DYST, no MDD	45.8	45.8	1. CT 2. Fluoxetine	13 18	HDRS, BDI	No statistically significant differences between the groups	RCT, small sample size, pilot study	1–
Hollon et al. (2014) [104]	cMDD duration longer than 2 years (subsample)	43.2	58.8	1. CT + antidepressant 2. Antidepressant	452 (subgroup cMDD: 159 (35.2%)	HDRS	Superiority of combined treatment limited to the nonchronic MDD subsample. Comorbid Axis II disorders took longer to recover	RCT	1–
Keller et al. (2000) [27]	cMDD, MDD +DYST, rMDD incomplete recovery (duration longer than 2 years)	43.0	65.3	1. CBASP 2. CBASP + nefazodone 3. Nefazodone	228 227/220 226	HDRS	Equal efficacy of both monotherapies, superior outcome for combined treatment	RCT	1–
Kocsis et al. (2009) [114]	cMDD, MDD +DYST, rMDD incomplete recovery (duration longer than 2 years)	45.2	54.9	1 AD + CBASP 2. AD + SPT 3. AD	200 195 96	HRDS QUIDS	No differences between the study arms	RCT, augmentation study (non-responders)	1–
Lynch et al. (2003) [131]	MDD, outpatient	66	85	1. AD + RO-DBT 2. AD	34	HDRS BDI	Higher remission rate in the RO-DBT group	RCT, pilot study	1–
Markowitz et al. (2005) [125]	Early onset DYST, no MDD	42.3	63	1. IPT 2. SPT 3. IPT + sertraline 4. Sertraline	23 26 21 24	HDRS, BDI, CDRS	Superiority of pharmacotherapy and combined treatment over psychotherapy alone for response and remission, but underpowered	RCT, underpowered	1–
Miller et al. (1999) [102]	MDD + DYST	37.4	80.7	1. CBT + pharmacotherapy 2. SST + medication 3. Medication	6 8 5	M-HDRS, BDI	Combined treatment superior	RCT, small sample size, pilot study	1–
Schramm et al. (2008) [127]	cMDD	42.8	73.2	1. IPT + pharmacotherapy 2. Pharmacotherapy + CM	24 21	HDRS, BDI	Higher response and remission rates for IPT group	RCT, analysis of a subsample	1–
Schramm et al. (2011) [69]	cMDD, early onset	40.2	55.2	1. CBASP 2. IPT	14 15	HDRS-24 IDS-SR QIDS-C16	Equal efficacy in reducing observer rated depression, superior efficacy of CBASP in self-reported depressive symptoms, higher response and remission rates for CBASP in the ITT sample	RCT, pilot study	1–
Strauss et al. (2012) [149]	cMDD, MDD +DYST, rMDD incomplete recovery (duration longer than 2 years)	43	71.4	1. PBCT 2. TAU	28	BDI-II	Better improvement in PBCT group	RCT, pilot study	1–
Wiersma et al. (2014) [117]	cMDD, MDD +DYST, rMDD incomplete recovery	41.5	60.1	1. AD + CBASP 2. AD + CAU	67 72	IDS-SR MINI	No difference between CBASP and CAU for weeks 8, 16, 32, greater reduction in depressive symptoms at week 52	RCT, effectiveness study	1–

Table 3 (*Continued*)

Randomized controlled trials

Bibliographic citation	Inclusion criteria of CD	Age of patients, mean	Female patients %	Interventions /Comparison groups	Comparison groups (n)	Primary instrument/ Outcome measures	Main results	Study type and comments	Evidence level
Williams et al. (2000) [150]	DYST	41.5	77.8	1. PST 2. Paroxetine 3. Placebo	72 69 70	HSCL-D	Smaller benefits for PST	RCT	1–

Cohort studies, case series, open studies

Bibliographic citation	Inclusion criteria	Age of patients, mean	Female patients (%)	Interventions /Comparison groups	Comparison groups (*n*)	Primary instrument/ Outcome measures	Main results	Study type and comments	Evidence level
Barrett et al. (2001) [151]	DYST	44.1	63.9	1. PST 2. Paroxetine 3. Placebo	43 42 42	HSCL-D	Higher remission rate for paroxetine and PST-PC	Cohort study	2+
Brakemeier et al. (2015) [105]	CD	46.6	61.4	CBASP plus medication	70	HDRS-24 BDI-II	Significant improvement and large effect size; 81.5% responders, 44.5% remitters	Open pilot study, inpatients	2+
De Jong et al. (1986) [98]	MDD + DYST	36.6	70	1. BA + SST + CT 2. CBT 3. Non-specific control	10 10 10	HDRS BDI D-Scale	Highest response rate in the modified group, but small sample	Cohort study with high risk of confounding or bias	2–
Harpin et al. (1982) [103]	MDD mean duration 17.8 years, treatment refractory	42.0	41.7	1. CBT 2. Waiting list	6 6	HDRS, Wakefield scale	Only the treatment group improved	Cohort study, small sample size	2–
Hellerstein et al. (2001)	DYST, no current MDD	45.1	50	1. CIGP + fluoxetine 2. Fluoxetine	20 20	HDRS BDI CDRS	Higher response and remission rates in CIGP + fluoxetine group, but small sample and hence no statistical significance	Cohort study	2–
Klein et al. (2004) [109]	CD	38.2	60	CBASP	10	HDRS-17 BDI-II	60% response	Case series	3
Malogiannis et al. (2014) [147]	CD	26–56	100	ST	12	HDRS	60% remission	Single case series study	3
Markowitz et al. (2008) [126]	DYST + alcohol	38.4	31	1. IPT 2. SPT	14 12	HDRS, BDI, CDRS	IPT large and BSP moderate effect size in depression	Cohort study, pilot study, small sample size	2–
Ravindran et al. (1999) [96]	DYST, no MDD	21 to 54 years, mean NR	57.7	1. CBT + sertraline 2. CBT + placebo 3. Sertraline 4. Placebo	24 24 22 24	HDRS-17	Highest responder rate in the CBT + sertraline group, but underpowered	Cohort study	2+
Swan et al. (2014) [121]	CD	44	68	CBASP	74	HDRS-24 BDI-II BSI	Significant decrease of depressiveness	Cohort study with high risk of confounding or bias	2–

AD: antidepressant; BA: behavioural activation; BDI: Beck Depression Inventory; BSI: Brief Symptom Inventory; CAU: care as usual; CB: cognitive therapy; CBASP: cognitive behavioural analysis system of psychotherapy; CBT: cognitive-behavioural psychotherapy; CD: chronic depression; CDRS: Cornell Dysthymia Rating scale; CIGP: cognitive-interpersonal group psychotherapy; CM: clinical management; cMDD: chronic major depressive disorder; CT: cognitive therapy; DYST: dysthymia; GSI: Global Severity Index; HDRS: Hamilton Depression Rating Scale; HSCL-D: Hopkins Depression self-report Scale; IDS-SR: Inventory of Depressive Symptomatology, self-report; IPT: interpersonal psychotherapy; ITT: intent-to-treat; MADRS: Montgomery-Asberg Depression Rating Scale; MCBT: mindfulness-based cognitive therapy; MDD: major depressive disorder; MINI: Mini International Neuropsychiatric Interview; NR: Not rated; PBCT: person-based cognitive therapy; PST: problem-solving therapy; PST-PC: Problem-Solving Treatment for Primary Care; PT: psychotherapy; QIDS-C16: 16-item Quick Inventory of Depressive Symptomatology, clinician rated; QUIDS: Quick Inventory of Depressive Symptoms; RCT: randomized controlled trial; rMDD: recurrent major depressive disorder; RO-DBT: radical openness dialectical behavioural therapy; SPC: Scales of Psychological Capacities; SPT: supportive psychotherapy; SST: social skills training; ST: schema therapy; TAU: treatment as usual.

treatment" in inpatient care. The NICE quality standard from 2011 [90] recommends "further suitable psychological treatment" for people "who have been treated for depression who have residual symptoms or are considered to be at significant risk of relapse" (statement 13).

The German Association for Psychiatry and Psychotherapy (Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde, DGPPN) S3 guideline on unipolar depression (National disease management guideline) provides recommendations for psychotherapy in dysthymia, double depression and CD [87,91]. A new version of this guideline has been published very recently. According to the current version of the guideline, patients with double depression and CD should be advised that combination treatment with antidepressants and psychotherapy is more effective than monotherapy (recommendation Grade A). In dysthymia, psychotherapy should also be offered (recommendation Grade B). Long-term stabilizing psychotherapy (focus on recurrence prevention) should be offered to patients with an increased risk of relapse (recommendation Grade A) and patients with TRD should be offered an appropriate psychotherapy (recommendation Grade B). There is empirical evidence that psychotherapy (CBT, IPT and short-term PP) is effective in patients with a comorbid personality disorder (borderline, paranoid, anxious [avoidant] and dependent), either as monotherapy or in combination with pharmacotherapy. Furthermore, there is evidence that the combination of psychotherapy and pharmacotherapy is more effective than either pharmacotherapy or psychotherapy alone.

The "Practice Guideline for the Treatment of Patients with Major Depressive Disorder" from the APA [85] recommends strategies to address nonresponse (defined as not achieving at least moderate improvement within 4–8 weeks of treatment), such as reviewing contributing factors (diagnosis, psychosocial factors, side effects, therapeutic alliance, treatment adherence) and changing the treatment plan [85]. For patients in psychotherapy with nonresponse, the APA recommends that additional factors should be assessed, including the frequency of sessions and whether the specific approach to psychotherapy adequately addresses the patient's needs. Consideration should be given to increasing the intensity of treatment or changing the type of therapy. Combined treatment with psychotherapy and medication is recommended. So far, no specific APA guideline exists for chronic/persistent depression.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) states in its "Clinical Guidelines for the Management of Major Depressive Disorder in Adults" from 2009 [86] that Level 2 evidence supports CBASP as second-line monotherapy or "add-on" to antidepressants in the continuation and maintenance phases of treatment in depressive disorders. CBT and IPT continue to have the best evidence for efficacy, both in acute and maintenance phases of MDD. However, psychotherapy in CD is not evaluated separately.

So far, no Cochrane review has examined psychotherapy in CD. A few Cochrane reviews are available on the psychotherapeutic treatment of depression, such as "Behavioural therapies versus other psychological therapies for depression" [92] or "'Third wave cognitive and behavioural therapies versus other psychological therapies for depression" [93], but they address acute forms of depression.

One recent meta-analysis on psychotherapy for CD and dysthymia [80] included 16 studies in 2116 patients and concluded that psychotherapy has a small but significant effect on patients with dysthymia and CD ($d = 0.23$) compared to control groups. Psychotherapeutic methods comprised CBT, behavioural therapy, IPT, cognitive-interpersonal group therapy for CD, CBASP and SPT. Cuijpers et al. [80] found psychotherapy to be less effective than pharmacotherapy ($d = -0.31$), although this finding was fully attributable to the sample of dysthymic patients. The combined treatment showed higher effect sizes than pharmacotherapy ($d = 0.23$) or psychotherapy ($d = 0.45$) alone. Moreover, the effect size was correlated with the number of psychotherapeutic treatment sessions and at least 18 sessions have been suggested to be needed for achieving an optimal effect, because each extra session increased the effect size by 0.04 [80]. The authors also hypothesised that while sudden improvement ("sudden gains") during psychotherapy of depression, which normally occurs between the eighth and tenth session, predict a better outcome for non-chronic depressed patients, gains of psychotherapy treatment may take longer in CD and are more gradual than sudden. Psychotherapy appears to be less effective in CD and dysthymia than it is in non-chronic depressive disorders [80]. Therefore, there is a special need for further research on how psychotherapeutic methods should be adapted for this group of patients. In a previous series of meta-analyses Cuijpers et al. found that psychotherapy (CBT, IPT, PST, non-directive SPT and behavioural activation therapy) was effective for the subsample of patients with CD, but that effects were smaller than for non-chronic forms of depression [94].

One network meta-analysis on acute treatments for PDD [81] included 60 trials (dysthymic and chronic depressive patients). The authors of this meta-analysis state that IPT without additional medication was less effective than medication alone, but IPT combined with medication was marginally superior to medication in CD, although not in dysthymia. For CBASP, no significant differences in efficacy compared with medication were found, with or without additional medication. Because a large amount of between-trial heterogeneity was observed, further conclusions were restricted to pair-wise between-trials comparisons. The authors concluded that medication would be the most preferable option in dysthymia, but that CBASP might be effective in dysthymia as well [81]. They further concluded that IPT combined with medication showed efficacy, whereas CBASP plus medication "can be recommended only with weak to moderate strength" because of conflicting results [81]. Overall, the authors give a moderate recommendation for CBASP in PDD. This meta-analysis also showed that efficacy varies with symptom severity and that both severity and chronicity may play a specific role in effect size [81].

An earlier meta-analysis by Imel et al. [95] on unipolar depression and dysthymia included 28 studies on psychotherapy and medication. Both psychotherapy and medication were found to be effective during treatment and did not significantly differ post-treatment. In dysthymia, medication showed a small advantage over psychotherapy. Psychotherapy showed better results during follow-up; the results were significantly influenced by the length of follow-up, suggesting a possible prophylactic effect of psychotherapy.

The systematic review and meta-analysis by von Wolff et al. [79] found small but significant effects of combined treatment (psychotherapy plus pharmacotherapy) and a higher quality of life under combined therapy. Psychotherapeutic trials included CBT, CBASP, SPT and IPT. No differences regarding long-term effects were observed between combined treatment and pure pharmacological interventions. However, only 5 studies provided data for follow-up (mean 12.5 months) after the end of acute treatment.

The systematic review by Spijker et al. [78] of 10 RCTs (in a total of 2316 patients with CD) indicated that the best evidence for the treatment of CD is available for the combination of psychotherapy, especially CBASP, and antidepressant pharmacotherapy. One of their conclusions was that evidence for both monotherapies is very weak, though insufficient data are available.

5. Psychotherapeutic treatment for chronic depression: review of studies

5.1. Cognitive-behavioural therapy (CBT)

CBT is one of the most studied and best validated psychotherapy approaches. It nowadays focuses on the interaction between behaviour, thoughts and emotions and is based on robust knowledge about learning and reinforcement or extinction. CBT uses a wide array of interventional strategies including modification of behaviour, cognitive strategies and interpersonal techniques. CBT is very well evaluated in the treatment of depression. Some older studies also examined the efficacy of CBT in CD patients. However, all of the studies had severe methodological limitations. Ravindran et al. [96] used a double-blind design to examine 97 pure dysthymic patients (medication free) randomized to 12 weeks of either placebo ($n = 50$) or sertraline ($n = 47$). Moreover, patients received either weekly 90-minute sessions of group CBT (25 of the drug-treated and 24 of the placebo-treated patients), implemented with the CBASP technique of situational analysis (SA), or no additional CBT (22 of the drug-treated and 26 of the placebo-treated patients) [96]. Treatment with sertraline, with or without group CBT, reduced the clinical symptoms of dysthymia. The reductions were similar in the drug plus CBT group and in participants who received the drug alone. Furthermore, while group CBT alone reduced the depression scores, this effect was not significantly greater than the effect of the placebo. Drug treatment also induced marked improvement in functional measures; these effects were augmented in some respects by group CBT. In the combination group (sertraline plus CBT), 70.8% responded (defined as a 50% decrease of the 17-item Hamilton Depression Rating Scale [HDRS-17] score and a score of ≤ 10), in the sertraline-only group, 54.5%, and in both the CBT plus placebo condition and the placebo-only conditions, 33.3%. There was a higher percentage of responders in the combination group than in the sertraline-only group, but the difference was not statistically significant. The CBT group had no more responders than the placebo-only group. However, the authors noted that this result must be interpreted cautiously because the study was underpowered and the duration of treatment short.

In a study by Hellerstein et al. [97], 40 dysthymic outpatients were treated with either fluoxetine alone or fluoxetine and 16 sessions of cognitive-interpersonal group psychotherapy for chronic depression (CIGP-CD), which combined cognitive and interpersonal approaches (controlled study). Those who responded to an initial period of 8 weeks of fluoxetine were allocated to supplementary group psychotherapy ($n = 8$) or continued medication only ($n = 11$). The loss of participants from termination to follow-up was 26%. Results are limited because of the small sample size and because differences were not statistically significant and therefore have to be interpreted with caution. At the end of the treatment period, 89% of the patients in the combined treatment condition had responded (defined as 50% decrease in HDRS-17 scores and 1 or 2 points on the Clinical Global Impressions [CGI] improvement subscale), while 76% of the fluoxetine-only group had responded. At follow-up (week 28, 32 and 36) 61% of combined treatment patients and 40% (6/15) of medication-only patients had responded. After treatment, 82% (14/17) of the combined treatment participants and 63% (10/16) of the fluoxetine-only participants were in remission (defined as a score of 0 on the HDRS-17 item number 1 and no longer meeting DSM-IV criteria for dysthymia); at follow-up 31% (4/13) and 50% (6/12), respectively, were in remission.

De Jong et al. [98] compared 2 forms of a CT program adapted for CD and a waiting list condition over a period of approximately 11 weeks in 30 medication-free patients (inpatients) with double depression. Patients were sequentially assigned in a non-randomized manner to 1 of the 3 groups (cohort study). Participants completed:

- 20 to 25 individual 50-minute sessions of therapy, including cognitive restructuring and activity scheduling, supplemented with 10 to 12 90-minute sessions of social competence training in a group format (COMB condition) or;
- CT with cognitive restructuring alone in 45 to 50 individual 50-minute sessions (CR condition) or;
- a non-specific waiting list for 2 months (WL).

Response was defined by the following criteria: post-treatment Beck Depression Inventory (BDI) score ≤ 14 or $> 50\%$ reduction in the pre-treatment BDI score, $> 50\%$ reduction in the pretreatment Inpatient Multidimensional Psychiatric Scale (IMPS) score, and $> 50\%$ reduction in the pretreatment IMPS D-score. Patients were called responders if they met at least 2 of these 3 criteria. Sixty percent of those in the COMB group responded whereas only 30% of those in the CT group and 10% of those in the WL group did. Chi-square analysis revealed a significantly superior response to COMB. However, the authors did not reach definite conclusions regarding the most effective type of intervention because multiple types of interventions were combined in the COMB group only. Another limitation is that the authors did not use the HDRS for primary outcome analysis, but a combination of the IMPS and the BDI.

A few other earlier pilot studies on CBT in CD, dysthymia or double depression found inconsistent results ranging from no difference between treatment group and placebo [99,100] and no better results with CBT compared to pharmacotherapy [101] to superiority of the CBT group compared to the waiting list [102], especially when combining CBT with social skills training [103].

When considering early studies on CBT, one has to take into account that all the studies applied modifications of standard CBT approaches, i.e. they were all enriched with training for social interaction. In addition, most of those earlier studies were underpowered, included primarily dysthymic patients, had very short treatment periods and used response instead of remission rates as primary outcomes. Therefore, because of these methodological limitations the findings of superiority of combination treatment (CBT and pharmacotherapy) over CBT alone or pharmacotherapy alone need to be interpreted with caution.

One more recent study investigated 452 outpatients with a diagnosis of MDD and a subgroup of 159 patients with chronic MDD (35.2%) [104]. Patients were randomly assigned to CT (not particularly tailored for CD) plus antidepressant medication or to antidepressant medication alone. The authors found that the superiority of the combined treatment of psychotherapy was limited to the non-chronic MDD subsample and was not found in the chronic MDD subsample. Moreover, patients with comorbid axis II disorders took longer to recover than patients without comorbid axis II disorders, regardless of the condition.

A sequential approach is supported by 1 recent study [105]. Ninety inpatients with MDD (46.7% of whom had CD) were treated with right unilateral ultra-brief acute ECT. ECT responders received 6 months guideline-based antidepressant medication and were randomly assigned to add-on therapy with group CBT (CBT arm), add-on therapy with ultra-brief pulse continuation ECT (ECT arm) or no add-on therapy (MED arm). The group psychotherapy was enriched by the SA technique from CBASP. The main finding indicates that group CBT in combination with antidepressants might be an effective continuation treatment to sustain response after successful ECT in MDD patients [105].

5.2. Cognitive-behavioural analysis system of psychotherapy (CBASP)

CBASP, a psychotherapeutic method developed by James McCullough [63,106], is the only treatment that has been specifically tailored for early-onset CD. Based on the assumption that early interpersonal trauma has resulted in dysfunctional mechanisms of derailed affective and motivational regulation and a reduction of perceived functionality, the main objective in CBASP is learning to recognize the consequences of one's own behaviour for other people and develop social problem-solving skills and empathy to reach desired outcomes. Single case reports were published as early as the 1980s, but it took a considerable amount of time until the concept became known across Europe and the United States [106–108]. CBASP combines elements from CBT with interpersonal and psychodynamic strategies [109–111] with a focus on the interpersonal outcome and is intended to teach the patient to develop interpersonal awareness, empathy and goal-oriented favourable behaviour.

Because over recent years a considerable number of studies have been conducted on CBASP in CD, we have subdivided this section to facilitate readability, as follows:

- randomized controlled trials of CBASP vs. antidepressant medication;
- randomized controlled trials of CBASP vs. antidepressant medication vs. comparator psychotherapy;
- randomized controlled efficacy trials of CBASP vs. comparator psychotherapy;
- open studies/case series.

Whereas efficacy trials test psychotherapy under ideal standard conditions to study the question of proof of antidepressant action, effectiveness trials investigate study populations under real-life conditions to investigate the question of a wider clinical relevance of effects.

5.2.1. Randomized controlled trials of CBASP and antidepressant medication

A large randomized controlled multi-centre study in CD ($N = 681$) was conducted by Keller et al. [27] at 12 sites across the United States and used CBASP for its psychotherapy arms. It compared the effectiveness of 12 weeks of nefazodone alone ($n = 226$), CBASP individual therapy alone ($n = 228$) and the combination of both ($n = 227$). Patients in the CBASP-alone and combined-treatment groups received about 12-16 sessions of psychotherapy. Both active conditions showed lower recurrence rates. In the first 4 weeks of acute treatment, patients receiving medication only and those receiving combined treatment showed a faster rate of response than those receiving psychotherapy only. After week 4, the reduction of symptoms was most pronounced in the combined treatment group. The response rates in the medication and CBASP monotherapy groups converged to show a similar course from week 8 onwards. The combined treatment group showed the best outcome at week 12 and this treatment was superior to both monotherapies (overall rates of response in modified intention-to-treat [ITT] sample: 73% for the combined treatment, 48% for nefazodone alone and 48% for CBASP alone).

Subsequent to this important primary publication, numerous post hoc analyses from this study were published. The results of the most relevant publications are summarized in Table 4.

The main trial also implemented a crossover phase for non-responders to monotherapies (CBASP: $n = 61$; nefazodone: $n = 79$) [112] and patients in both arms showed a clinical benefit from the switch strategy. Moreover, the study had a long-term continuation phase, during which 12 monthly sessions were added to the acute treatment phase. In this continuation phase, 82 patients who had responded to CBASP in the acute treatment phase were randomly assigned to either once-monthly CBASP sessions or assessment appointments [109]. In the CBASP condition, significantly fewer patients experienced recurrence than in the assessment only condition.

As described above, 1 study [27] found that CBASP was as effective as nefazodone; however, nefazodone has been removed from the market. A recent bi-centre study (Schramm et al. [113], published after closure of our literature search and not included in the database for evidence grading and the Delphi process) compared CBASP with escitalopram. Sixty patients with CD were randomized to CBASP (22 sessions) or escitalopram plus clinical management (ESC/CM). The primary outcome measure was the Montgomery-Asberg Depression Rating Scale (MADRS) score, assessed by blinded raters, after 8 weeks of treatment. In case of non-improvement ($< 20\%$ reduction in MADRS score), the other treatment condition was added for the subsequent 20 weeks of extended treatment. The ITT analysis revealed that clinician- and self-rated depression scores decreased significantly after 8 and 28 weeks and found no significant differences between the 2 rating methods. Response rates after 28 weeks were high (CBASP: 86.2%, ESC/CM: 93.3%), remission rates moderate (CBASP: 31.0%, ESC/CM: 46.7%) and improvement in global functioning and quality of life significant; none of the differences between the groups was significant. After being augmented with the respective other condition, non-improvers to the initial treatment caught up with initial improvers in terms of depression scores and response and remission rates by the end of treatment.

5.2.2. Randomized controlled trials of CBASP vs. antidepressant medication vs. other psychotherapy

In another large trial on CBASP by Kocsis et al. [114] (REVAMP study), a total of 808 patients with CD across 8 academic sites received 12 weeks of open-label antidepressant medication according to a pharmacotherapy algorithm similar to the STAR*D study (phase 1) [115]. Patients who had not or had only partially responded after 12 weeks received all next-step pharmacotherapy options with or without adjunctive psychotherapy (phase 2) and were assigned to 1 of the following 3 treatment conditions for another 12 weeks: a medication switch or augmentation ($n = 96$), supplementary CBASP ($n = 200$; mean of 12.5 CBASP sessions) or supplementary SPT as active control condition ($n = 195$). The randomization was stratified according to whether patients achieved remission or partial response in phase 1. About 40% of the non-responders in the first 12-week phase later remitted within the second 12-week phase. No differences were found between the treatment arms. Remission rates at week 24 were defined by an HAM-D score < 8, an HAM-D score reduction $\geq 50\%$ from baseline and a Clinical Global Improvement score of 1 or 2 for 2 consecutive visits. Remission rates were 39.5% in the medication augmentation or switch group, 38.5% in the medication plus CBASP group and 31.0% in the medication plus SPT group. These findings were critically discussed [116] on the basis of the study design: the study may have selected patients with a preference for drug treatment, because the design guaranteed receiving antidepressant medication but did not guarantee receiving psychotherapy. Also, the low number of CBASP and SPT psychotherapy sessions was criticized. The follow-up phase for this study has yet to be published.

5.2.3. Randomized controlled efficacy trials of CBASP vs. comparator psychotherapy

A pilot RCT compared CBASP with IPT as another depression-specific approach [69]. Thirty non-medicated patients with early-onset CD were randomly allocated to 22 sessions of individual IPT or CBASP over 16 weeks. Observer-rated blinded

Table 4
Reanalysis of the Keller study on the cognitive behavioural analysis system of psychotherapy (CBASP).

Bibliographic citation	Main results
Hirschfeld et al., 2002 [156]	Psychosocial functioning was best in the combined treatment condition
Zajecka et al., 2002 [157]	Significant improvement in sexual interest/satisfaction and sexual function (female) across all treatment groups. Combined treatment produced greater improvement than CBASP alone, but was not significantly different from medication alone
Nemeroff et al., 2003 [158]	Patients with early interpersonal trauma benefited more from CBASP than from medication. The combined treatment condition was not significantly better than CBASP alone in those with a history of trauma. In a later erratum, the authors state that improvement of HAMD scores was relative to the first week of treatment instead of baseline. When change scores relative to baseline are used, the interaction effects between treatment type and childhood trauma histories were not statistically significant. However, CBASP outperformed pharmacotherapy regarding remission rates in the subgroup of chronic depressives with childhood trauma
Gelenberg et al., 2003 [159]	Psychotherapy during acute and continuation treatment enhanced the initial response but was not associated with lower recurrence rates. After one year recurrence rates were higher in the medication group than in the placebo group
Manber et al., 2003 [160]	Only medication alone compared to CBASP alone improved early morning awakening and total sleep time
Klein et al., 2004 [161]	The authors examined the efficacy of the cognitive-behavioral analysis system of psychotherapy (CBASP) as a maintenance treatment for chronic forms of MDD. Eighty-two patients who had responded to acute and continuation phase CBASP were randomized to monthly CBASP or assessment only for 1 year. Significantly, fewer patients in the CBASP than assessment-only condition experienced a recurrence. The 2 conditions also differed significantly on change in depressive symptoms over time. These findings support the use of CBASP as a maintenance treatment for chronic forms of MDD
Schatzberg et al., 2005 [162]	Reanalysis of the cross-over phase (ITT sample): 156 monotherapy non-responders completed the initial acute-phase trial and 140 (89.7%) consented to begin the alternate treatment. Twelve of the 73 patients initially treated with nefazodone stopped the crossover treatment, while 4 of the 83 patients who initially received CBASP declined to proceed with crossover to nefazodone. The mean number of psychotherapy sessions attended during the crossover phase was 16.5. Both the switch from nefazodone to CBASP and the switch from CBASP to nefazodone resulted in statistically significant improvement. Neither the rates of response nor the rates of remission were significantly different when the groups of completers were compared However, the switch to CBASP after nefazodone therapy was associated with significantly less attrition because of adverse events, which may related to the higher intent-to-treat response rate among those crossed over to CBASP (57% vs 42%)
Arnow et al., 2007 [163]	Of 681 randomized study participants, 156 were defined as dropouts. Dropout rates were equivalent across the three treatments. Dropouts attributed to medication side effects were significantly lower in COMB than in MED, suggesting that the relationship with the psychotherapist may increase patient willingness to tolerate side-effects associated with antidepressant medications
Constantino et al., 2008 [164]	Submissive chronically depressed patients improved significantly regarding their interpersonal style: the patients' interpersonal impacts on their therapists changed in adaptive, theoretically predicted ways by the end of a 12-week CBASP concept
Kocsis et al., 2009 [165]	Treatment effect varied as a function of preference and was particularly apparent for patients who initially expressed preference for one of the monotherapies
Stulz et al., 2010 [166]	A growth mixture model (GMM) was used to examine differential treatment effects in patient subgroups. Combination treatment was significantly superior to the two monotherapy arms in those patients with moderate to severe depression
Constantino et al., 2012 [167]	Decreases in patients' hostile-submissive impact messages were significantly associated with reduction of depression

measurements (HDRS-24) did not differ between the groups; however, self-reports differed significantly, with lower BDI scores in the CBASP arm. In the ITT sample, both post-treatment response rates (defined as HDRS-24 $\leq$ 15 and 50% decrease) and remission rates (defined as HDRS-24 $\leq$ 8) were significantly lower in the IPT arm (26.7% responders, 20.0% remitters) than in the CBASP arm (64.3% responders, 57.1% remitters). The authors concluded that CBASP showed significant advantages over IPT in the group of early-onset and mostly early-traumatized CD patients and assumed that the specific strategies tailored to approach the therapeutic relationship explained most of the difference.

Wiersma et al. recently published a one-year effectiveness RCT of CBASP (n = 67) versus care as usual (CAU, n = 72) in chronically depressed patients [117]. The study was performed at 3 outpatient clinics in the Netherlands. CAU consisted of psychotherapy treatments generally offered to CD patients at these sites (CBT: 53%, n = 38; IPT 25%, n = 18; short psychoanalytic SP: 10%, n = 7; supportive/structured therapy: 7%, n = 5; pharmacotherapy only: 5%, n = 4). Patients attended a mean of 24 CBASP sessions or 23 sessions of CAU and more than 60% of the patients received supplementary pharmacotherapy. Participants were assessed with the self-report version of the Inventory of Depressive Symptomatology (IDS-SR) at baseline and weeks 8, 16, 32 and 52. Response was defined as a 50% symptom reduction in the IDS-SR and remission as an IDS-SR score below 13. The groups did not differ significantly at baseline or the first 3 measurement points. At week 52, however, the CBASP group had improved significantly more than the CAU group (effect size: 1.37) and a medium effect size was detected between the groups (CBASP vs. CAU $d = -0.55$). In the completer sample, rates of responders (CBASP: 41.2%, CAU: 18.9%) and remitters (CBASP: 26.0%, CAU: 9.4%) differed between the groups, but in the ITT sample, no differences were found for either response (CBASP: 31.3%, CAU: 21.1%) or remission (CBASP: 19.4%, CAU: 9.9%). Dropout rates were high but the same in both groups, and dropouts did not differ on baseline demographic and clinical variables. Patients received a diagnostic interview with the Mini International Neuropsychiatric Interview-plus (MINI plus) at baseline and at the end of the study. CBASP completers were less likely to fulfil DSM-IV criteria for major depression than CAU completers (CBASP: 26.1% vs. CAU: 65.3%) at week 52. This result remained significant in the ITT analysis (CBASP: 49.3% vs. CAU: 76.4%) [117].

An 8-week RCT by Michalak and Schramm [118] examined the effects of group MBCT and treatment as usual (TAU), group CBASP and TAU and TAU alone in 106 chronically depressed patients. CBASP was significantly more effective than TAU in reducing depressed symptoms assessed with the HRSD-24 whereas MBCT was not more effective than TAU (study published after closure of literature search and not included in the database for evidence grading and the Delphi process).

In a German multicentre trial of CBASP for unmedicated patients with early-onset CD [119], SPT was chosen as a credible active comparator. Each treatment comprised 24 50-minute sessions in the acute treatment phase (20 weeks) followed by 8 sessions of extended treatment (28 weeks). Nine sites enrolled 268 patients with early-onset CD. Final results are expected to be published in 2016. A naturalistic 2-year follow-up is currently being conducted to evaluate likely carry-over effects of both approaches.

5.2.4. Open studies and case series with CBASP

Brakemeier et al. [120] (see also the pilot study for this project [107]) conducted an open, 12-week effectiveness study on inpatients ($n = 70$) with CD. Treatment consisted of up to 24 individual sessions of CBASP and twice weekly group sessions; CBASP elements were also integrated into other treatments provided by the local multidisciplinary team. Patients were assessed with the HDRS-24 and Beck Depression Inventory (BDI)-II before and after treatment. HDRS-24 scores decreased from a mean of 31.07 (SD 6.27) to 12.43 (SD 7.25), with a large effect size of $d = 2.52$ (ITT sample). BDI-II scores were similar and decreased from a mean of 33.22 (SD 9.73) to 18.83 (SD 12.74), with an associated effect size of $d = 1.15$. Response was defined as a decrease of at least 50% on the HDRS-24 and remission as a score of 10 or less on the HDRS-24. Remission rates at discharge were 43.1% and responder rates were 81.5% in the completer sample. Six months after discharge, 75.0% of the responders showed sustained response and 25.0% had relapsed; 12 months after discharge the rates were 48.0% and 52.0%, respectively.

Swan et al. [121] recently published an open naturalistic outpatient study in which 74 chronically depressed patients received CBASP on an individual basis over a 6-month period and attended on average 18.5 h of therapy. HRSD-24 scores decreased significantly in the completer and ITT groups and the effect size was large (completer sample: $d = 1.7$). Scores on the BDI-II showed the same pattern, with an effect size of $d = 1.03$. Response and remission criteria were adopted from the study by Keller et al. [27]. According to the HDRS-24, 30.4% ($n = 14$) of participants met remission criteria and 30.4% ($n = 14$) met response criteria; depressive symptoms improved in 60.8% of the completer sample and 38.0% of the patients with baseline data (ITT sample). Scores on instruments of quality of life, social functioning and interpersonal functioning also improved significantly in the study. However, the study shows some serious weaknesses in that most of the patients received additional medication and the evaluations were not performed by independent raters.

Another small prospective open study focused on the effects of CBASP on neural functioning [122]. Ten patients with CD received 12 weeks of CBASP and functional magnetic resonance imaging (fMRI) and performed an emotional processing task at baseline and after the 12 weeks. The authors reported a response rate to treatment of 60% and demonstrated increased arousal to negative emotional expressions compared with healthy volunteers. Moreover, patients showed an increase in left amygdala reactivity during implicit processing of emotional expressions after psychotherapy.

5.3. Interpersonal psychotherapy (IPT)

IPT [123] may be a promising treatment option for patients with CD because it focuses on interpersonal problems as one of the main challenges in the treatment of this patient group. In IPT, interpersonal problems are considered to be a factor contributing to the genesis and maintenance of depression. In 2 studies in dysthymic outpatients the combination of IPT and psychopharmacotherapy outperformed IPT alone and medication alone [124,125]. However, both studies have marked methodological limitations. Browne et al. [124] analysed 707 dysthymic patients in a single-blind, randomized clinical trial. Patients were assigned to either sertraline alone (50–200 mg), IPT alone (10 sessions) or sertraline plus IPT. In the acute treatment phase (first 6 months), all groups received full active treatment followed by an additional 18-month naturalistic follow-up phase. Response rates (40% improvement of MADRS) were 60.2% for sertraline alone, 46.6% for IPT alone and 57.5% for sertraline plus IPT. In the follow-up phase, both sertraline alone and sertraline plus IPT were more effective than IPT alone. Markowitz et al. [125] studied 94 pure dysthymic patients in a randomized 16-week trial of IPT, SPT, sertraline and sertraline plus IPT. Participants improved in all conditions, whereby response and remission rates were higher for sertraline with or without IPT than for psychotherapy alone. Response rates were 58% for sertraline alone, 57% for combined treatment, 35% for IPT and 31% for SPT. However, the study did not reach the calculated sample size and was therefore underpowered. It also lacks follow-up data.

IPT has also shown its effectiveness in inpatient settings. In a pilot study, Markowitz et al. compared the treatment effects of 16-week IPT with SPT for dysthymic disorder and alcohol abuse in 26 patients [126]. IPT had a large and SPT a moderate effect size in depression, whereas SPT had a moderate and IPT a small effect size in percentage of days abstinent. However, the results have to be considered with caution because of the small sample size.

In a subgroup analysis by Schramm et al. [127], 45 inpatients with cMDD were randomly allocated to IPT (15 individual and 8 group sessions) plus pharmacotherapy or to medication plus clinical management (CM) for 5 weeks. In the ITT analysis, both groups had achieved significant and large improvements at week 5 (IPT: $d = 3.57$; CM: $d = 1.98$) and response rates (defined as 50% decrease on the HDRS-17) were significantly higher in the IPT group (70.8%) than in the CM group (38.1%), as were remission rates (defined as ≤ 7 on the HDRS-17) (IPT group: 50.0%; CM group: 28.6%). However, differences in remission rates were only statistically significant in the completer sample and not in the ITT sample. Global functioning also improved significantly in both conditions, while the medication plus IPT group achieved a statistically better outcome on global functioning in the between-group analysis. Schramm et al. conducted a second outpatient pilot study to compare IPT with CBASP [69]. This study, which is described above, found that IPT was somewhat effective for patients with early-onset depression but not as effective as CBASP.

Another study in 35 outpatients with dysthymic disorder (91% had comorbid MDD) found better results for a combination treatment of IPT-D (IPT adapted to dysthymic disorder) and pharmacotherapy over 48 weeks than pharmacotherapy alone with routine care [128].

5.4. Radically open dialectic behavioural therapy (RO-DBT)

Lynch [129] adapted Dialectical Behaviour Therapy (DBT), which was originally evaluated for borderline personality disorder, for CD and named the new approach for the treatment of disorders of overcontrol "radically open dialectical behaviour therapy" (RO-DBT). RO-DBT is based on the assumption that patients with treatment-resistant or chronic forms of depression are sensitive to threat but insensitive to reward. They prefer order and structure over novelty, have strong tendencies for constraint and show covert expression of hostility. These are factors contributing to poor interpersonal relationships and an inability to adapt to changing circumstances. RO-DBT skills training consists of a core module on radical openness–in which dysfunctional behaviours are targeted such as low openness, heightened threat sensitivity or low validation of others–and modules on mindfulness training, interpersonal effectiveness, emotion regulation and distress tolerance [130].

To date, earlier versions of RO-DBT have been evaluated in 1 pilot study [130]. In a 28-week study, Lynch et al. randomly allocated 34 mainly chronically depressed older patients aged 60 and above to 2 treatment groups, an antidepressant medication-only condition and a medication plus modified weekly DBT skills group combined with an additional weekly telephone coaching session [131]. After treatment, remission rates assessed with the BDI (criterion of ≤ 9) were 50% in the DBT-augmented patients and 42% in the medication-only group. The difference was

even larger when assessed with the HDRS (criterion of ≤ 7), with remission rates of 71% in the medication plus DBT group and 47% in the medication only group.

Moreover, a 5-year multisite RCT is currently being conducted to compare RO-DBT and standard care (mainly antidepressant medication) and thus investigate the efficacy and mechanisms of RO-DBT for patients with treatment-resistant and CD [132].

5.5. Psychodynamic psychotherapy (PP) and psychoanalytic treatment

In brief, PP and psychoanalytic treatment are widely applied psychotherapy approaches that focus mainly on unconscious processes and interactive patterns between the patient and the therapist (transference) in an effort to reveal unconscious motives and conflicts in order to alleviate mental tension or suffering. Core features of psychodynamic thinking and therapeutic technique include:

- interventions focusing on the interpretation of the patient's unconscious conflicts as they emerge in the transference relationship;
- a focus on affect as it emerges in relationships, attempts to avoid distressing thoughts, memories of past events and recurring patterns of interactions.

Different methods exist and vary with respect to setting, frequency, length of therapy and therapeutic techniques, ranging from brief dynamic therapy to classical psychoanalysis. The effectiveness of short-term PP for depressive disorders was recently confirmed in a meta-analysis by Driessen et al. [133]. Long-term psychotherapy and investigation whether treatment may prevent future symptom recurrence or a chronic illness course [134] are of special importance in CD. The effectiveness of long-term PP for general mental disorders has been demonstrated in several independent studies, 1 review [135] and 2 meta-analyses [136,137]. An overview of successful treatment components of short-term psychodynamic treatment for depressive disorders and modules of a unified psychodynamic protocol were recently provided by Leichsenring and Schauenburg [138]. Using fMRI, Buchheim et al. [139] demonstrated treatment-specific neurobiological changes in circuits implicated in emotional reactivity and control after long-term PP.

With respect to CD, 2 studies [134,140] and 1 reanalysis [141] included CD patients only as a subgroup. We have not considered these studies for evidence grading and recommendations, because of the mixed samples (CD and episodic types of MDD). However, these studies provide the most substantial data available in the field of PP and psychoanalysis, so we will describe their designs and patient samples to outline the state of research. Clearly there is an urgent need for further RCTs that investigate PP and psychoanalysis in CD.

Huber et al. [134] investigated a mixed sample of 66 patients with chronic or non-chronic depression. The patients had a diagnosis of unipolar MDD or double depression (subsample of patients with double depression: $n = 36$; 54.2%) and were treated with psychoanalytic psychotherapy or PP ($n = 35$ patients in the psychoanalytic group, $n = 31$ in the psychodynamic group).

Huber et al. [140] conducted another study to compare psychoanalytic psychotherapy, PP and CBT at pre- and post-treatment and 3-year follow-up in 100 patients with a diagnosis of MDD or double depression (subsample of patients with double depression: $n = 55$; 55%). After 3 years, psychoanalytic psychotherapy and CBT differed significantly (OR = 4.79; 96% CI), with a higher reduction of depressive symptoms for psychoanalytic psychotherapy (remission rate measured by BDI: 83%) when compared to CBT (remission rate 52%). PP (remission rate 68%) did not significantly differ from CBT. However, no data on the subgroup of double depression are available. A recent reanalysis of this study by Zimmermann et al. [141], compared psychoanalytic therapy (i.e., high-dose LTPP) with psychodynamic therapy (i.e., low-dose LTPP) and CBT in patients with a diagnosis of MDD or double depression (subsample of patients with double depression: $n = 40$; 51.95%) to examine whether the effectiveness of LTPP is due to distinctive features of psychodynamic/psychoanalytic techniques or to a higher number of sessions. The main result showed that not duration but application of psychoanalytic techniques was responsible for the more favourable outcome of psychoanalysis. The mean duration of depression was similar in all trials (65.5, 61.7 and 67.5 months, respectively) [134,140,141] and therefore many of the patients included might be considered as having a chronic form of depression. None of the trials published separate data for CD subgroups, but further analysis of these groups would be of interest.

Another study in CD patients was published very recently [142] and a further one is currently underway. The Tavistock Adult Depression Study [142] (study published after closure of literature search and not included into database for evidence grading and the Delphi process) tested the effectiveness of long-term psychoanalytic psychotherapy (LTPP) as an adjunct to treatment as usual according to UK national guidelines (TAU), compared to TAU alone, in patients with long-standing major depression who had failed at least 2 different treatments and were considered to have treatment-resistant depression. Patients ($N = 129$) were recruited from primary care and randomly allocated to the 2 treatment conditions. They were assessed at 6-monthly intervals during the 18 months of treatment and at 24, 30 and 42 months during follow-up. The primary outcome measure was the 17-item version of the Hamilton Depression Rating Scale (HDRS-17), with complete remission defined as a HDRS-17 score ≤ 8 and partial remission defined as a HDRS-17 score ≤ 12. Secondary outcome measures included self-reported depression as assessed by the Beck Depression Inventory-II, social functioning as evaluated by the Global Assessment of Functioning, subjective well-being as rated by the Clinical Outcomes in Routine Evaluation - Outcome Measure, and satisfaction with general activities as assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire. Complete remission was infrequent in both groups at the end of treatment (9.4% in the LTPP group vs. 6.5% in the control group) as well as at the 42-month follow-up (14.9% vs. 4.4%). Partial remission was not significantly more likely in the LTPP than in the control group at the end of treatment (32.1% vs. 23.9%, $P = 0.37$), but significant differences emerged during follow-up (24 months: 38.8% vs. 19.2%, $P = 0.03$; 30 months: 34.7% vs. 12.2%, $P = 0.008$; 42 months: 30.0% vs. 4.4%, $P = 0.001$). Both observer-based and self-reported depression scores showed steeper declines in the LTPP group, alongside greater improvements on measures of social adjustment. These data suggest that LTPP can be useful in improving the long-term outcome of treatment-resistant depression.

In the ongoing study, called "Die Langzeittherapie bei chronischen Depression (LAC) Studie" ["Long-term therapy in chronic depression (LAC) study", authors' translation], Beutel et al. [143] are investigating long-term CBT and psychodynamic or psychoanalytically oriented treatment (PAT) in 420 patients with CD at several study centres across Germany. Patients are allowed to choose treatment according to their preference (CBT or PAT) or, if they have no clear preference, are randomized to CBT or PAT. In the first year of treatment, the dose is comparable in both therapy groups, i.e. either up to 80 sessions of PAT or up to 60 sessions of CBT. If patients do not have a clear preference, they are randomized

to 1 of the 2 conditions. After the first year, PAT can be continued in a "naturalistic" way, i.e. according to the usual method of treating such patients in the German health care system (normally 240 to 300 sessions over 2 to 3 years). CBT therapists may extend their treatment up to 80 sessions, but should focus mainly on maintenance and relapse prevention. The authors plan a total of 240 patients to complete the investigations (60 patients each assigned to CBT or PAT according to the patient's preference and 60 patients each randomized to CBT or PAT) and to perform a total of 11 assessments throughout the treatment and follow-up period (up to 3 years after initiation of treatment). The primary outcome measures are the Quick Inventory of Depressive Symptoms (QIDS, independent clinician rating) and the BDI after the first year.

5.6. Schema therapy (ST)

ST, originally developed by Jeffrey Young [144] to treat patients who usually fail classical CBT, i.e. patients with personality disorder, is an integrative approach largely based on the Beck approach, with cognitive, behavioural, experiential and psychodynamic elements. In MDD, ST has shown comparable efficacy to CBT [145]. Renner et al. [146] presented an ST treatment protocol for chronically depressed patients. In a single case preliminary study, the effectiveness of ST was evaluated in 12 patients with CD over a treatment period of up to 60 sessions (the first 55 sessions were offered weekly, the last 5 biweekly) and at the 6-month follow-up [147]. Remission was defined as an HRSD score < 8 at the post-treatment and follow-up assessments; response was defined as a reduction of 50% in the HRSD and a score ≤ 15 but > 8 at post-treatment and follow-up assessments. About 60% of patients ($n = 7$) either remitted or responded after up to 60 sessions of ST. The mean HRSD decreased from 21.07 at baseline to 9.40 at post-treatment and 10.75 at follow-up.

5.7. Mindfulness-based cognitive therapy (MBCT) and person-based cognitive therapy (PBCT)

MBCT is a fairly recent approach to behaviour therapy that includes meditation practice and cognitive elements. A pilot study by Barnhofer et al. [148] that compared 2-hour MCBT group sessions plus TAU with TAU alone (TAU: antidepressant medication, psychological interventions, GP consultation, visit by psychiatric nurse) over 8 weeks found a statistical difference in the response rate in the ITT sample as measured with the BDI-II (defined as BDI-II ≤ 13 and 50% decrease): 37% of participants in the MBCT arm ($n = 14$) responded compared to 6% in the TAU arm ($n = 14$). Patients with current depressive symptoms and a history of at least 3 previous episodes of depression and suicidal ideation were included in the study sample and randomized.

PBCT is an integration of CT and mindfulness. A pilot study by Strauss et al. examined the effectiveness of PBCT in 28 outpatients with CD [149]. Twelve weeks of PBCT as a 90-minute group psychotherapy ($n = 11$) were compared with TAU (details not specified, $n = 12$), and a reliable change in depression was found. In the completer sample, 64% of the participants in the PBCT group showed reliable improvement and none showed reliable deterioration; no participants in the TAU group showed reliable improvement, while 18% showed reliable deterioration.

5.8. Problem-solving therapy (PST)

PST focuses on the development of coping skills to improve the patient's ability to manage difficult life situations. So far, no studies have specifically focussed on PST in CD. However, 2 older randomized trials investigated the effectiveness of PST in dysthymic patients. Williams et al. found no significant difference between the PST and placebo groups [150], whereas Barrett et al. found a higher remission rate with PST than with placebo [151].

6. Recommendations

6.1. Selection of studies as the evidence base for the European Guidance Project

The systematic literature search led us to agree on 5 recommendations. However, this selection has some limitations:

- only studies published in English or German were included;
- the search for studies included in the evidence base ended January 2015, so important recent studies have not been included in the database underlying our recommendations (Table 3), although we nevertheless briefly report on these studies to inform our readers;
- a general publication bias, which also impacts on our selection, cannot be completely excluded because no meta-analytic methods were used to assess this issue.

An important controversial issue was the question whether evidence in psychotherapy studies can reach the same 1+ to 1++ level (very low risk or low risk of bias) as drug trials do. Investigating psychotherapy in RCTs does not allow double-blind designs, and expectations of patients, therapists and raters (if not blinded for the condition and measurement time point) may constitute a source of bias, which cannot be as strictly controlled as in RCTs of pharmacological interventions. Thus, we decided to conservatively grade even high quality RCTs comparing at least 2 treatment arms (psychotherapies, medication or combined treatment) as 1− (high risk of bias). This means, however, that the highest grade of recommendation needs to be formally based on meta-analyses rather than single RCTs.

6.2. Proposed recommendations of the European Guidance Project

6.2.1. Recommendation 1: choice of psychotherapy

The EPA Guidance Group on Psychotherapy in CD considers CBASP and, to a lesser degree, IPT focussing on interpersonal problems to be effective in CD. Consequently, psychotherapeutic treatment specifically aimed at the common characteristics of CD should be first choice. CBASP is recommended as first-line treatment for CD (evidence level: 1++; recommendation grade: A) and IPT is recommended as second-line treatment (evidence level: 1; recommendation grade: B).

Evidence for efficacy of CBT in CD is limited; the interpretation of previous studies is hampered by their methodological limitations. Because all CBT variants studied in CD included training with an interpersonal focus, differences between CBT and CBASP/IPT might be notably smaller than reported. Taken together, CBT is recommended as third-line treatment (evidence level: 2+, recommendation grade: C).

Psychodynamic and psychoanalytic treatment are considered by experts to be effective interventions in CD; however, this view is based on RCTs in mixed populations that included CD and non-CD types of MDD and case series in CD. RCTs or cohort and case-control trials in CD only were lacking and a first RCT specifically focussing on CD has just been published. Thus, higher standard trials, which are currently underway (or published, but not included in our search because of the date of publication), are urgently needed. The EPA Guidance Group recommends psychodynamic and psychoanalytic treatment as a third-line treatment on the basis of studies mixing CD and episodic MDD as well as on clinical experiences of respected experts in the field (evidence level: 3–4; recommendation grade: D). PST, ST, RO-DBT and MCBT

are also recommended as third-line treatments, because there is less empirical support for them and not enough trials have been conducted. Present studies have methodological limitations (evidence level: 2− to 1−; recommendation grade: C) and efficacy needs to be proven in larger trials.

Moreover, the type of psychotherapy should be individually chosen in consideration of early versus late onset, type of depression, number of episodes, early trauma, symptom severity, patient preference and comorbid personality disorder (evidence level: 4; recommendation grade: Good Practice Point [GPP]). Therefore, the treatment of CD requires a differentiated diagnostic evaluation of chronicity.

6.2.2. Recommendation 2: psychotherapy or pharmacotherapy?

The EPA Guidance Group on CD considers both psychotherapy and pharmacotherapy to be effective in CD (psychotherapy of short duration is less effective in pure dysthymia) and recommends both approaches (evidence level: 1+; recommendation grade: A). Combined treatment with psychotherapy and pharmacotherapy has been reported to be superior to psychotherapy or pharmacotherapy alone (evidence level: 1+; recommendation grade: A) and should therefore be the first choice. The only exception is pure dysthymia, where the current evidence does not support an advantage of combined treatment. Pharmacotherapy should be individually chosen in consideration of anxiety levels, sleep problems and obsessive-compulsive symptoms. If a patient prefers monotherapy, the EPA Guidance Group recommends pharmacotherapy or psychotherapy to the same degree (evidence level: 1+, recommendation grade: A).

6.2.3. Recommendation 3: personalized treatment

The EPA Guidance Group recommends a personalized approach based on the patient's preferences and needs, e.g. pharmacotherapy or psychotherapy, group or individual psychotherapy, in- or outpatient treatment (evidence level: 4; recommendation grade: GPP).

6.2.4. Recommendation 4: psychotherapy "dosage"

The EPA Guidance Group considers effect sizes of psychotherapy in CD to be associated with the psychotherapy "dosage", i.e. the number of sessions provided in a certain time frame (evidence level: 1+; recommendation grade: A). Psychotherapy should be offered in the acute phase and be of adequate length and frequency. Psychotherapy treatment gains for CD may take longer than for patients with recurrent MDD and may be more gradual than sudden. Sessions should be conducted at least once a week (evidence level: 4, recommendation grade: GPP). For relapse prevention, psychotherapeutic interventions should include follow-up sessions (evidence level: 4, recommendation grade: GPP).

6.2.5. Recommendation 5: limitations and future research

The EPA Guidance Group concludes that there are limited data for many promising therapeutic interventions, e.g. ST, RO-DBT and psychodynamic or psychoanalytic treatment in CD. This lack of evidence does not mean that these interventions lack efficacy. Rather, there is a lack of trials, especially RCTs, on the long-term effect and outcome of psychotherapy and of trials investigating predictive factors for therapy response. There is an urgent need for further RCTs and personalized approaches with the main focus on which psychotherapy works for which type of depression.

A major problem is the inhomogeneous definition of chronicity and differing outcome measures used in the studies included in this guidance paper; this problem hampers the use of meta-analytic methods to compare psychotherapeutic approaches. Therefore, future research should use a homogenous definition of CD. At the very least, the 2-year criteria of chronicity should be given. Moreover, future research should address the direct comparison between group and individual therapy as well as in- and outpatient settings. The sustainability of effects, particularly compared to pharmacotherapy, has also not yet been studied.

A possible publication bias should always be taken into account and is also a limitation of systematic reviews such as this guidance paper. Moreover, expectations of patients, therapists and raters may constitute a source of bias in psychotherapy research, as may patients' preference for psychological rather than pharmacological treatment.

7. Conclusion

The development of disorder-specific psychotherapy such as CBASP is an important approach to treating CD; additional forms of psychotherapy are currently being developed specifically for CD. The new DSM-5 classification has been another important step towards a better understanding and treatment of this complex affective disorder. However, ICD-10 is still missing an option to code for a chronic course of depression. Attention should be paid to the differences between patients with acute episodic depressive disorder and those with CD. Patients with CD may need specific and intensive psychotherapeutic support because of the association of CD with childhood trauma and attachment deficits and the comorbidity with personality disorders. Patients with CD should be offered specific psychotherapeutic approaches that address the interpersonal needs of these patients. Trials on the long-term effects and outcome of psychotherapy are lacking.

Most studies included in this review found that the combination of psychotherapy and pharmacotherapy has an additive effect compared to psychotherapy alone. However, some large studies did not find evidence for superiority of combination treatment in CD [104,114]. Therefore, treatment should be chosen in accordance with the patient's treatment preferences and a personalized approach should be considered, including individual factors such as severity of depression and type of CD. CD might be treated with sequential approaches, providing different types of treatment in different phases of illness on the basis of the current symptomatology [105,112,152,153]. Moreover, a more integrative model addressing biological, psychological and social problems could help to improve not only patients' depressive symptoms but also social functioning and quality of life.

In this guidance paper, we have highlighted individual psychotherapy. However, other forms of psychological support are relevant for CD, such as group therapy, inpatient programs, psychosocial interventions, multifamily interventions, family psychotherapeutic interventions, couple therapy and family and supportive networks, all of which have to be considered in future psychotherapy approaches.

Disclosure of interest

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